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Breast feeding and its association with childhood leukemia: A retrospective case-control study among children attending King Abdulaziz University Hospital in Jeddah, Saudi Arabia

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ABSTRACT

Objectives: Breastfeeding has a protective impact upon many diseases. However, limited evidence exists on the association between breastfeeding and childhood leukemia. Therefore we investigated this relationship among children attending King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia. *Methods*: This retrospective case-control study included children attending KAUH from 2008 to 2019. We compared 74 children diagnosed with leukemia with 148 age- and sex-matched controls. *Results*: Significantly longer breastfeeding duration occurred in cases (15 months) than in controls (12 months). Breastfeeding duration and pattern were not associated with reduced childhood leukemia risk. Antenatal exposure to pesticides and amphetamine consumption, intrapartum pain killer use, and child exposure to pesticides increased childhood leukemia prevalence. Higher socioeconomic status and higher level of parental education, preconception oral contraceptive pill use, supplemental folate use during pregnancy, and mothers' exposure to general anesthesia during delivery were associated with decreased childhood leukemia risks. *Conclusion*: Breastfeeding duration and practice were not associated with childhood leukemia, possibly because breastfeeding is widely practiced in Saudi Arabia. Future studies are needed to further explore the effects of breastfeeding on childhood leukemia.

Keywords: Acute lymphoblastic leukemia, acute myeloid leukemia, breastfeeding, childhood leukemia, Saudi Arabia

1. INTRODUCTION

Leukemia is the most prevalent pediatric (age, 0-14 years) malignancy worldwide (Steliarova-Foucher et al., 2001). Acute lymphoblastic leukemia (ALL) is the most commonly observed subtype, seen in 80% of all cases, whereas acute myeloid leukemia (AML) accounts for only 15% of all cases (Whitehead et al., 2016). Leukemia is the most commonly reported pediatric cancer type among the nationals of the Gulf Cooperation Council States aged between 0 and 14 years (33.4% among boys and 32.5% among girls) (Madouj et al., 2011). Additionally, the Saudi Cancer Registry reported that childhood cancers account for approximately 5.9% of all cancer cases in Saudi Arabia (Al-Shahrani et al., 2017). Leukemia accounts for 34.1% of the total number of cancer cases among Saudi children (Al-Mutlaq et al., 2015).

Although previous studies have focused on pediatric leukemia, the precise etiology remains unclear in most cases (Amitay and Keinan-Boker, 2015). Several risk factors, including those that affect mothers, such as the presence of infections, smoking, and exposure to ionizing radiation and pesticides, have been identified. Birth weight, exposure to ionizing radiation and pesticides, and the presence of congenital anomalies in children are also related to pediatric cancers (Spector et al., 2015). However, despite the remarkable improvements in the diagnostic and treatment techniques for the disease, leukemia continues to be the number one cause cancer-related death in children and adolescents aged 15-29 years, accounting for 13% of the total number of cancer-related deaths in this age group (Miller et al., 2020). Since infection is a risk factor for childhood leukemia, many researchers have investigated the effect of breastfeeding on leukemia prevention, given its immunity-boosting benefits (Amitay and Keinan-Boker, 2015). Breastfeeding confers passive direct immunity to the infant and exerts anti-inflammatory effects through the antimicrobial proteins, immunoglobulins, and maternal white blood cells that it contains. The aforementioned components play a criticalpart in the development and maturation of an infant's immunity (Lewis et al., 2017).

Data on the protective effects of breastfeeding against childhood leukemia are conflicting; some studies reported a risk reduction in breastfed children (Amitay and Keinan-Boker, 2015; Gao et al., 2018), while others did not find an inverse relationship between breastfeeding and the incidence of leukemia (Karimi et al., 2016; Rafieemehr et al., 2019). Although the overall survival rate associated with pediatric leukemia has increased overtime, it is still considered to have the highest malignant disease burden in Saudi children (Madouj et al., 2011).

No previous studies in Saudi Arabia have investigated the relationship between breastfeeding and leukemia, and none have focused on children living in Jeddah, in particular. Accordingly, we aimed to determine the association between breastfeeding and leukemia among children attending King Abdulaziz University Hospital in Jeddah, Saudi Arabia.

2. MATERIALS AND METHODS

Study design, participants, and eligibility criteria

This retrospective case-control study recruited patients who attended King Abdulaziz University Hospital, Jeddah, Saudi Arabia from 2008 to 2019. Initially, 104 children diagnosed with leukemia (both ALL and AML) aged 1-19 years were identified from the electronic medical record system of King Abdulaziz University Hospital. The diagnosis of leukemia was confirmed through bone marrow aspiration and immunophenotyping. Thirty children were excluded (8 patients with congenital disease, 11 with primary tumors before the age of 1 year, and 11 whose mothers could not remember the exact pattern and duration of breastfeeding or refused to participate). Therefore, 74 children with leukemia (cases) were included in the final analysis (34 girls and 40 boys).

The control group included 148 children (68 girls and 80 boys) who were matched for age and gender at a ratio of 1:2. Children in the control group were referred by those in the casegroup, and they included their relatives or neighbors. In the case of missing or unmatched controls, controls were recruited from among those attending the pediatric clinic for acute conditions, such as gastroenteritis, bronchial asthma, and tonsillitis.

Exposure assessment

A telephone interview was conducted with the mothers of the children classified as cases and controls to obtain data on their breastfeeding habits (duration and pattern), potential confounders, including the preconception, conception, and post-conception history regarding exposure to petroleum products, excessive use of paint in the house, use of hair dye during pregnancy, residence in an industrial area, exposure of parents and children to ionizing radiation, use of pesticides at home, gestational infections, and birth weight. Data on the family's educational and socioeconomic background were also collected. The data collection sheet was validated through a pilot study that included 30 participants. Its content was reviewed by multiple experts in the field at the pretest stage.

Ethical considerations

This study was approved by the ethics committee at King Abdulaziz University Hospital, Jeddah, Saudi Arabia (reference number, 334-19). Informed consent was obtained verbally from the mothers of all the participants during the telephone interview. The confidentiality of all the participants' information was strictly maintained. Anonymity was assured to all the participants.

Statistical analysis

Data were entered and analyzed using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA). Results are presented as mean (standard deviation). Categorical variables are reported as frequency (percentage). Independent t-test was used for the comparison of the means of different continuous variables in the case and control groups. Chi-square test with risk estimate was used to determine the association between the outcome (case or control) and different exposures. Odds ratios (ORs) with their 95% confidence intervals (CIs) are reported. A P-value <0.05 was considered significant.

3. RESULTS

In total, 74 cases and 148 controls, comprising 120 boys and 102 girls, were included in the final analysis. There were 40 (54.1%) boys and 34 (45.9%) girls in the case group, and 80 (54.1%) boys and 68 (45.9%) girls in the control group. The majority of the cases (n=69; 93.2%) were diagnosed with ALL; five (6.8%) participants in the case group had AML. Among the 74 cases, 65 (87.8%) were alive and 9 (12.2%) passed away. The mean age at the time of diagnosis of the cases was 5.3 (±3.6 standard deviation) years. The characteristics of the study groups are shown in Table 1.

Table 1 Characteristics of the study groups

Variable	Cases n=74 Mean ±SD	Controls n=148 Mean ±SD	P-value
Age (years)	8.6±4.5	8.6±4.8	0.992
Mother's age at time of conception (years)	26.6±6.4	29.1±6.2	0.007
Father's age at time of conception (years)	34.0±7.6	34.3±7.2	0.777
GA (weeks)	37.2±1.5	36.7±2.5	0.050
BW (kgs)	2.94 ±0.63	2.78±0.74	0.090
Duration of BF (months)	15.0 ±8.3	11.7±8.4	0.009

Abbreviations: SD; standard deviation, GA; gestational age, BW; birth weight, BF; breast feeding

There were no major variabilities in terms of age (at the time of the data analysis), gestational age at delivery, or birth weight. The mothers of the children in the case group were significantly younger at the time of conception than those of the controls. The duration of breastfeeding was significantly longer in the case group (15 months) than in the control group (12 months, P=0.009). The association was between breastfeeding habits and leukemia. The majority of the cases (92%) and controls (86%) were breastfed. Breastfeeding (P=0.23) or the pattern of breastfeeding (P=0.25) did not show a significant association with leukemia (Figure 1, Table 2).

The results of the univariate analysis have focusing on the association between childhood leukemia and different risk factors. A higher monthly income (OR=0.153, 95%CI=0.074–0.312) and a higher level of education in both parents (OR=0.183, 95%CI=0.091–0.368 [mother]; OR=0.278, 95% CI=0.152–0.507 [father]) were significantly associated with a decreased risk of leukemia (Figure 2, Table 2).

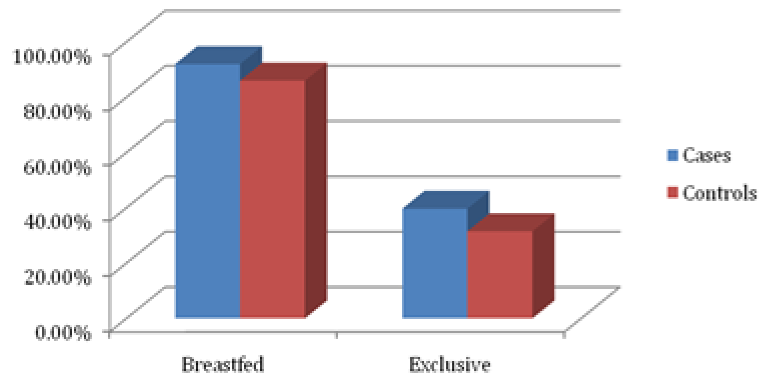

Figure 1 Breastfeeding habits among cases and controls

Table 2 Odds ratio, 95% confidence interval and univariate analysis of breastfeeding habits other risk factors and their association with childhood leukemia.

Risk factors	Cases n (%)	Controls n (%)	OR	95%CI	p-value
Was the child ever breastfed					
Yes	68 (92.0%)	126 (86.0%)	1.799	0.69–4.693	0.225
No	6 (8.0%)	20 (14.0%)	Reference		
Pattern of breast feeding					
Exclusive	27 (39.7%)	39 (31.5%)	1.435	0.775–2.658	0.249
Not exclusive	41 (60.3%)	85 (68.5%)	Reference		
Monthly income					
≥5000	11 (14.9%)	79 (53.4%)	0.153	0.074–0.312	<0.001
<5000	63 (85.1%)	69 (46.6%)	Reference		
Mother's level of education					
University and above	12 (16.2%)	76 (51.4%)	0.183	0.091–0.368	<0.001
High school and below	62 (83.8%)	72 (48.6%)	Reference		
Father's level of education					
University and above	21 (28.4%)	87 (58.8%)	0.278	0.152–0.507	<0.001
High school and below	53 (71.6%)	61 (41.2%)	Reference		
Family history of cancer					
Yes	26 (35.6%)	45 (30.8%)	1.282	0.707–2.326	0.412
No	47 (64.4%)	101 (69.2%)	Reference		
Cancers in the neighborhood					
Yes	4 (7.4%)	14 (11.1%)	0.640	0.201–2.042	0.448
No	50 (92.6%)	112 (88.9%)	Reference		
Consanguinity between parents					
Yes	29 (39.2%)	53 (35.8%)	1.155	0.650–2.053	0.623
No	45 (60.8%)	95 (64.2%)	reference		

History of miscarriage					
Yes	17 (23%)	44 (29.7%)	0.705	0.369–1.345	0.288
No	57 (77%)	104 (70.3%)	Reference		
History of stillbirth					
Yes	5 (7.5%)	12 (8.1%)	0.914	0.309–2.707	0.871
No	62 (92.5%)	136 (91.9)	Reference		
Order of the child					
1st	19 (25.7%)	53 (35.8%)	Reference		
2nd & above	55 (74.3%)	95 (64.2%)	0.619	0.333–1.152	0.128

Abbreviations: OR; odds ratio CI; confidence interval

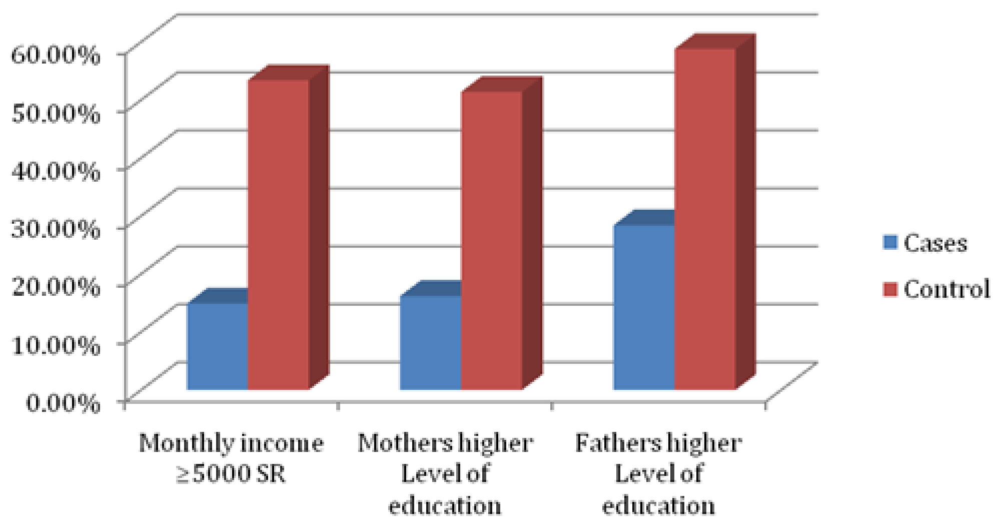

Figure 2 Socioeconomic status among cases and controls

Other risk factorswere divided into those related to the preconception period are presented in (Table 3). During the preconception period, a history of contraceptive pill use (OCP) was conversely associated with leukemia (OR=0.498, 95% CI=0.275–0.902). Risk factors that were related to the pregnancy period presented in (Table 4). During pregnancy, mothers' exposure to pesticides (OR=2.652, 95%CI=0.991–7.096) and use of amphetamine (OR=3.898, 95%CI=1.085–14.004) were associated with a significantly increased risk of childhood leukemia. In contrast, the intake of supplemental folate during pregnancy was notably associated with a reduced risk of the disease (OR=0.181; 95%CI=0.076–0.430). These significant findings are represented in (Figure 3).

Table 3 Univariate analysis of preconception risk factors and their association with childhood leukemia

Risk factors	Cases n (%)	Controls n (%)	OR	95% CI	p-value
Use of OCP					
Yes	22 (29.7%)	68 (45.9%)	0.498	0.275–0.902	0.020
No	52 (70.3%)	80 (54.1%)	Reference		
Ionizing radiation to mother					
Yes	7 (9.9%)	10 (7.1%)	1.433	0.521–3.938	0.484
No	64 (90.1%)	131 (92.9%)	Reference		

Ionizing radiation to father					
Yes	4 (5.8%)	8 (5.7%)	1.015	0.295–3.496	0.602
No	65 (94.2%)	132 (94.3%)	Reference		
History of exposure to petroleum products					
Yes	8 (11.8%)	11 (8.1%)	1.503	0.575–3.931	0.404
No	60 (88.2%)	124 (91.9%)	Reference		

Abbreviations: OR; odds ratio CI; confidence interval OCP; oral contraceptive pills

Table 4 Univariate analysis of risk factors during pregnancy and their association with childhood leukemia

Risk factors-	Cases n (%)	Control n (%)	OR	95%CI	p-value
Maternal infection					
Yes	7 (9.5%)	19 (12.8%)	0.709	0.284–1.772	0.461
No	67 (90.5%)	129 (87.2%)	reference		
Ionizing radiation to the fetus					
Yes	1 (1.4%)	1 (0.7%)	2.000	0.123–32.432	0.559
No	73 (98.6%)	146 (99.3%)	Reference		
Active smoking					
Yes	8 (10.8%)	16 (10.8%)	1	0.407–2.456	1
No	66 (89.2%)	132 (89.2%)	Reference		
Exposure to painting in the house					
Yes	4 (5.8%)	12 (8.8%)	0.641	0.199–2067	0.453
No	65 (94.2%)	125 (91.2%)	Reference		
Mother use of hair dye					
Yes	8 (12.1%)	14 (10.2%)	1.212	0.481–3.050	0.683
No	58 (87.9%)	123 (89.8%)	Reference		
Living near industrial site					
Yes	2 (2.7%)	4 (2.7%)	0.993	0.178–5.550	0.679
No	72 (97.3%)	143 (97.3%)	Reference		
Exposure to pesticide					
Yes	9 (16.4%)	9 (6.9%)	2.652	0.991–7.096	0.046
No	46 (83.6%)	122 (93.1%)	Reference		
Use of amphetamine					
Yes	7 (13.7%)	4 (3.9%)	3.898	1.085–14.004	0.033
No	44 (86.3%)	98 (96.1%)	Reference		
Use of folate					
Yes	32 (62.7%)	93 (90.3%)	0.181	0.076–0.430	<0.001
No	19 (37.3%)	10 (9.7%)	Reference		

Abbreviations: OR; odds ratio, CI; confidence interval

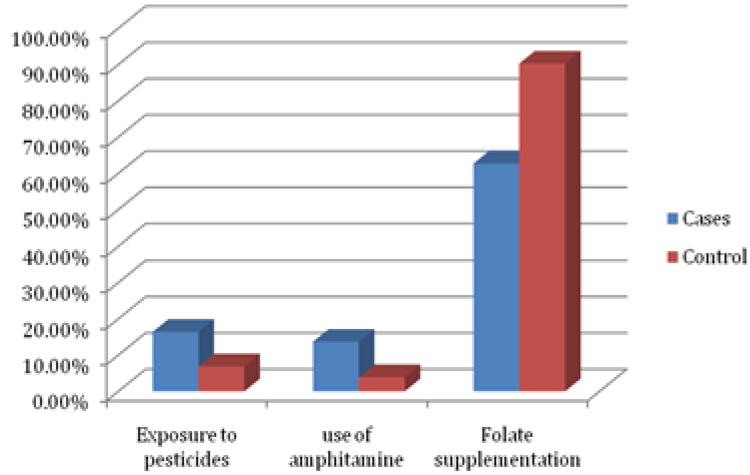

Figure 3 Antenatally risk factors significantly associated with leukemia among cases and controls

Risk factors related to the delivery and post-partum periodsare presented in (Table 5). The use of pain killers during delivery was significantly found to increase the likelihood of childhood leukemia (OR=1.925, 95%CI=1.094–3.387), while the exposure of mothers to general anesthesia during delivery was associated with a decreased risk of the disease (OR=0.282; 95%CI=0.120–0.666). Children with a history of pesticide exposure were seven times (95% CI=1.44–37.61) more likely to have leukemia (P=0.011) than those without the history.

Table 5 Univariate analysis of postpartum risk factors and their association with childhood leukemia

Risk factors	Cases n (%)	Controls n (%)	OR	95%CI	p-value
Mode of delivery					
C-section	17 (23%)	51 (34.9%)	0.556	0.293–1.053	0.072
SVD	57 (77%)	95 (65.1%)	Reference		
Use of pain killers during delivery					
Yes	42 (56.8%)	60 (40.5%)	1.925	1.094–3.387	0.022
No	32 (43.2%)	88 (59.5%)	Reference		
Exposure to GA					
Yes	7 (9.5%)	40 (27%)	0.282	0.120–0.666	0.003
No	67 (90.5%)	108 (73%)	Reference		
Difficult labor					
Yes	8 (12.1%)	13 (9%)	1.401	0.551–3.561	0.478
No	58 (87.9%)	132 (91%)	Reference		
Neonatal jaundice					
Yes	14 (23.3%)	39 (27.5%)	0.804	0.398–1.623	0.542
No	46 (76.7%)	103 (72.5%)	Reference		
Supplemental oxygen					
Yes	9 (12.2%)	24 (16.4%)	0.704	0.309–1.603	0.401
No	65 (87.8%)	122 (83.6%)	Reference		

History of ionizing radiation					
Yes	1 (1.4%)	9 (6.2%)	0.209	0.026–1.678	0.095
No	73 (98.6%)	137 (93.8%)	Reference		
Passive smoking					
Yes	21 (28.4%)	38 (26%)	1.126	0.602–2.106	0.710
No	53 (71.6%)	108 (74%)	Reference		
Exposure to petroleum products					
Yes	3 (4.2%)	4 (2.8%)	1.5	0.327–6.890	0.437
No	69 (95.8%)	138 (97.2%)	Reference		
Living near industrial site					
Yes	3 (4.1%)	3 (2.1%)	2.043	0.402–10.381	0.318
No	70 (95.9%)	143 (97.9%)	Reference		
History of pesticide exposure					
Yes	6 (9.8%)	2 (1.5%)	7.364	1.443–37.610	0.011
No	55 (90.2%)	135 (98.5%)	Reference		

Abbreviations: OR; odds ratio, CI; confidence interval, SVD; spontaneous vaginal delivery, GA; general anesthesia

4. DISCUSSION

In this study, which investigated the association of breastfeeding with childhood leukemia in Jeddah, Saudi Arabia, we found that breastfeeding was not associated with a decreased risk of childhood ALL and AML. The number of breastfed children in the case group exceeded that of those in the control group and breastfeeding in the former was for a longer duration than that in the latter, although the difference was statistically insignificant. While these findings suggest that breastfeeding is practiced widely among the Saudi community and for a more sustained period than other populations, potentially in association with the Saudi religious and cultural background, other environmental or hereditary factors in Saudi Arabia may obscure its protective effects. Moreover, most patients were from families with low income; hence, the nutrient composition of the consumed breast milk and the biologically active components contained in it may have been compromised, resulting in a weaker protective effect against childhood leukemia (Boix-Amorós et al., 2019).

Our findings are in line with those previously observed in the Middle East, such as the results of a study conducted in 2019 by Rafieemehr et al., (2019), who reported that breastfeeding duration in Iranian children did not have any association or protective effect against ALL. A study by Karimi et al., (2016) found a similar result among Iranian children. However, a study conducted by Gao et al., (2018) among Chinese children showed that breastfeeding had a protective role. Amitay et al., (2016) revealed that breastfeeding for a period longer than 6 months was inversely correlated with the risk of childhood leukemia and lymphoma. On a larger scale, a meta-analysis of 17 studies concluded that breastfeeding for 6 months and more could prevent 14% to 20% of childhood leukemia cases (Amitay and Keinan-Boker, 2015). More over, Güngör et al., (2019) conducted an extensive and thorough systematic review on the relationship between breastfeeding and the risk of ALL. They concluded that breastfeeding has a slightly protective role against childhood leukemia. However, they confirmed that the present literature concerning the protective role of extended breastfeeding duration on ALL risks has limitations warranting further studies to define the protective impact of breastfeeding.

Mothers' consumption of amphetamine during pregnancy was noted to be directly correlated with a higher risk of leukemia in their offspring. Wen et al., (2002) confirmed an increased risk of ALL in children of parents who reported using these drugs before pregnancy as well as in children of mothers who used it during pregnancy. This could be attributed to the potential carcinogenic effects of amphetamine on N-rasoncogene of leukemic cells (Verstegen et al., 2020). In this study, the use of pain killer medications during labor was directly associated with the risk of leukemia in the delivered child. McKinney et al., (1999) detected an increased risk of childhood leukemia among the offspring of mothers who consumed opioids during pregnancy, although their finding was only tending toward significance. It has been determined that this phenomenon is related to the effect of opioids in regulating the transcription of tumor growth factors, upregulation of micro RNA, and oxidative stress (Kosciuczuk et al., 2020).

We also ascertained that the higher a family's socioeconomic status (high monthly income and high educational level for both parents), the lower the likelihood of childhood leukemia. Our results are consistent with studies conducted in the Middle East and internationally (Gao et al., 2018; Karimi et al., 2016). Families with a low monthly income are more likely to live in a disadvantaged residential area, which alters their access to health services and healthy foods and increases their vulnerability to environmental pollution (Flanagan et al., 2019). Moreover, low maternal education makes mothers more prone to working in a hazardous workplace, which may predispose them and their children to oncogenic damage (Janitz et al., 2017). Nevertheless, there is controversy surrounding this issue. Erdmann et al., (2020) noted that high socioeconomic status is a risk factor for childhood leukemia. This finding has been argued as having a possible bias due to the easy access to healthcare centers among those in the higher social status spectrum. Supplementary studies concentrating on the relationship between the socioeconomic status of the family and the risk of leukemia are required.

Children of mothers exposed to pesticides during pregnancy were three times more likely to develop leukemia than those whose mothers were not exposed to pesticides. Moreover, children exposed to pesticides were noted to be seven times more likely to develop leukemia than their unexposed counterparts. Thus, this study confirmed the previous findings regarding the association of exposure to pesticides during pregnancy and after with increased childhood leukemia risk (Van Maele-Febry et al., 2019). This finding may be ascribed to the ability of pesticides to generate chromosomal mutations in hematopoietic stem and/or progenitor cells (Hernández and Menéndez, 2016).

We also observed an inverse association between maternal OCP consumption and the risk of childhood leukemia in her subsequent children. However, this finding should be confirmed, as "mere chance" can be taken as a potential explanation. Conversely, a nationwide, population-based cohort study in Denmark (Hargreave et al., 2018) demonstrated an increased risk in the children of mothers who used hormonal contraception. This may be due to the fact that hormones may induce epigenetic changes in the ovum and cells during embryogenesis, leading to an oncogenic result (Hargreave et al., 2018). It is well-documented that the prenatal use of folic acid can reduce the risk of congenital anomalies in the fetus (van Gool et al., 2018) as well as the likelihood of developing childhood leukemia (Cantarella et al., 2017). The results of the present study confirm the aforementioned findings.

The current study suggests a relationship between the maternal exposure to general anesthesia during delivery and reduced risk of childhood leukemia. No previously published studies have examined or reported such an association. However, an association between the use of anesthetic agents and their effect on cancer cells activity and survival was suggested. This association was justified by changes in the stress response to the oprations or through effects on malignant cell signaling (Yooand Kim et al., 2020).

Strengths and limitations

This case-control study focused on the protective effects of breastfeeding against childhood leukemia in Jeddah, Saudi Arabia; no such study existed in Jeddah before now. This study's limitations include the low recruitment; out of 104 children diagnosed with ALL or AML, we were only able to recruit 74, making the sample size relatively small. Given that breastfeeding is highly practiced among the Saudi population, the small sample size may have obscured the detection of the protective effect of breastfeeding against childhood leukemia. Owing to the retrospective nature of the data collection method (interviews), an important concern was the recall bias associated with the measurement of breastfeeding duration, predominantly since the recall included data on events that occurred many years before the interviews took place. However, we believe that it is unlikely for this recall bias to have an enormous influence on our data, in view of the fact that only mothers served as informants and the interviews were conducted through the telephone. Moreover, since this was a single-center study, further multi-center studies should be conducted to verify our findings.

5. CONCLUSION

This study showed that neither breastfeeding practice nor its duration was associated with childhood leukemia in Jeddah, Saudi Arabia. This may be attributed to the fact that prolonged breastfeeding is a continuing habit and is religiously and traditionally valued and largely practiced in Saudi Arabia, compared with western countries. As this study is considered a preliminary investigation, prospective studies are essential further explore the relationship between breastfeeding and childhood leukemia. Since breastfeeding is widely practiced in Saudi Arabia, confirmation of other risk factors for the development of childhood leukemia is required to reduce the prevalence of childhood leukemia and its associated mortality.

Ethical approval

The study was approved by the Medical Ethics Committee of King Abdulaziz University (ethical approval code: 334-19).

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Authors' contributions
Abudaowd O: Acquisition of data, analysis and interpretation of the results, drafting of the final report, and provision of final approval of the version to be published.
AlJahdali G, AlKhotany B, AlSaaedi R, AlSiyoufi A, Subki S, AlTaifi R: Acquisition of data, drafting of the final report, and provision of final approval of the version to be published.
Al Kadi H: Conception and design of the study, analysis and interpretation of results, critical revision of the final report, and provision of final approval of the version to be published.

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Conflicts of interest
The authors declare that they have no conflict of interest.

Data and materials availability
All data associated with this study are present in the paper.

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